FDA Office of Generic Drugs Keynote Address:

UPDATE on GDUFA and FDA's Office of Generic Drugs

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Disclaimer

- This presentation reflects the views of the speaker and do not reflect official FDA, HHS, or other government opinion or policy.

- I have nothing to disclose.

OBJECTIVES

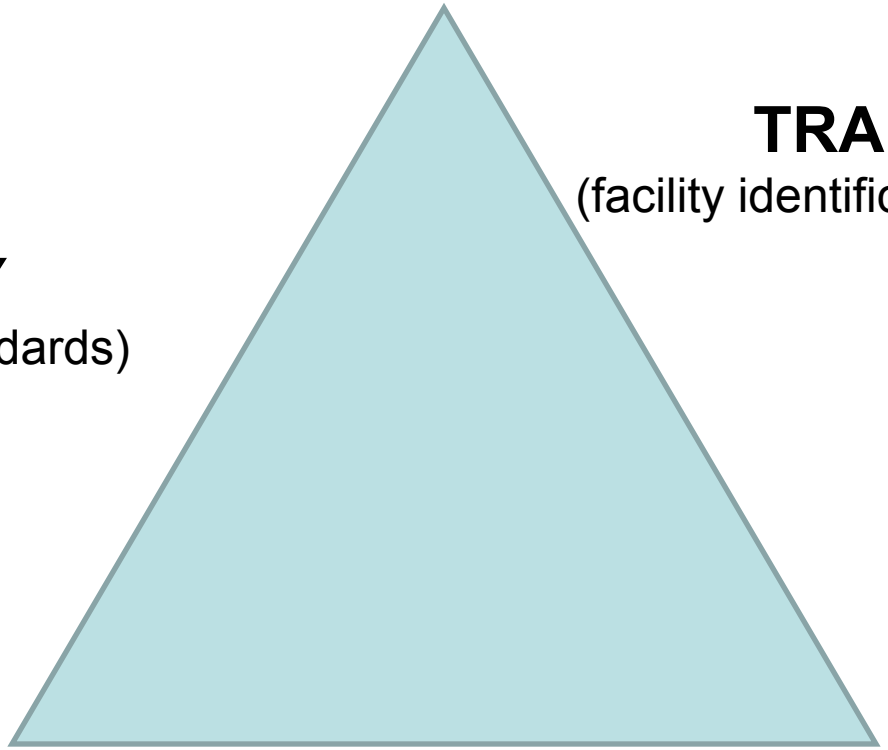
Provide updates:

1. GDUFA
   - Review goals/commitments
   - Changes
   - Accomplishments
2. Office of Generic Drugs (OGD)

GDUFA TENETS

TRANSPARENCY
(facility identification & communication)

SAFETY
(high quality standards)



ACCESS
(predictability & timeliness in review process)

GDUFA

- Increased:
  - Responsibility
  - Obligations
  - Commitments
  - Accountability
  - Quality
    - Applications, responses, communication
    - “Efficiency enhancements”

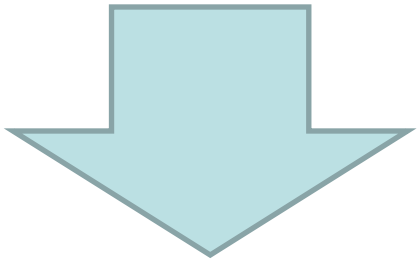
- For FDA **and** industry

GDUFA CHANGES

- **FDA Changes:**
  - Define Generic drug program
  - Review process
  - Communications, internal and external
  - Inspections
- **Industry changes:**
  - Quality of applications
  - Number of review cycles
  - Communication with FDA
  - Application chain integrity

GDUFA was/is a major GAMECHANGER

TRANSFORMATIONAL CHANGE

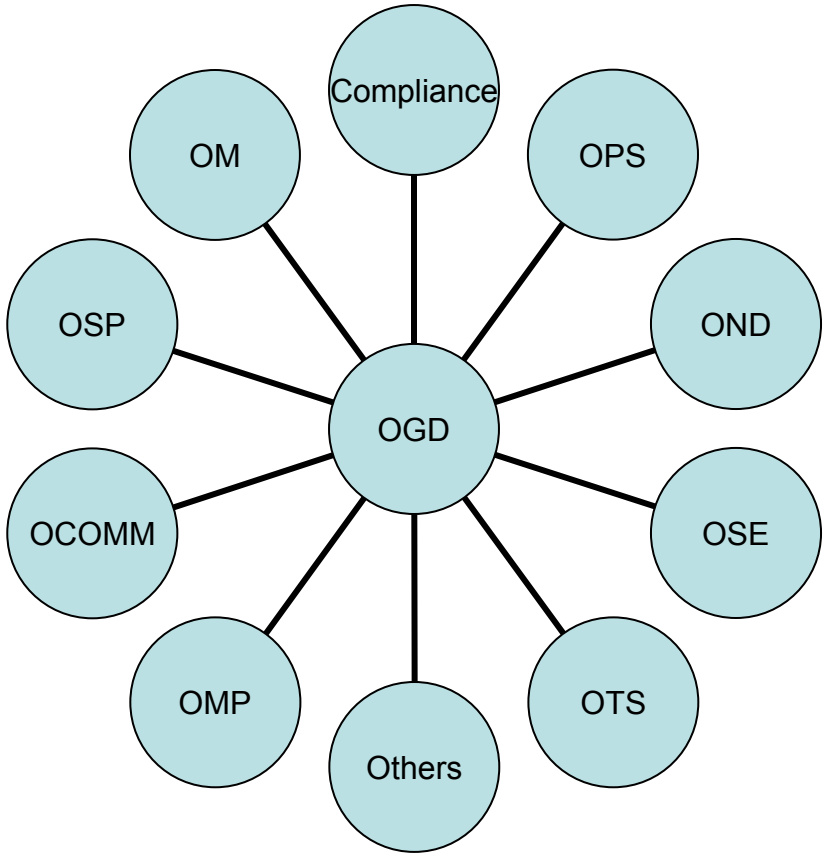


Professionalization of the generic drug program

GENERIC DRUG PROGRAM

- Not just OGD
- All of CDER
- Other FDA units:
  - ORA
  - Office of the Commissioner
  - CBER, CDRH

- OGD is the interface for ANDA applicants (industry) to interact with the Generic Drug Program



GDUFA

- High expectations, especially from industry
  - Paid fees, now you want and expect action
  - We hear you

- Current steps -
  - Operations & Implementation

GDUFA

- Success requires:
  - Process identification/mapping
  - Process improvement
  - Strategy to reach goals/metric
  - IT Systems Enhancements
  - Implementation & operationalization
  - Accountability

- Will not succeed if we throw additional resources (FTEs, $$) at it AND continue doing the same thing(s) as pre-GDUFA

TRADITION

JUST BECAUSE YOU'VE ALWAYS DONE IT THAT WAY
DOESN'T MEAN IT'S NOT INCREDIBLY STUPID.

GDUFA Goals & Commitments

1. GDUFA website

http://www.fda.gov/gdufa

2. GDUFA Goals/Commitment Letter

http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

5 BASICS ABOUT GDUFA

1. Goals apply to electronic submissions only
2. No small business waivers
3. It is a 5 year program with sequential and progressive implementation
4. By year 5, ANDA has 10 month review goal; results in Action (CR, TA, AP)
5. Paramount to meeting the goals, requires improved quality of applications/submissions

GDUFA Review performance goals

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Original ANDA	Expedite review of paragraph IV and maintain pre-GDUFA productivity		60% in 15 months	75% in 15 months	90% in 10 months
Tier 1 first major amendment	Maintain pre-GDUFA productivity		60% in 10 months	75% in 10 months	90% in 10 months
Tier 1 minor amendments (1st – 3rd)	Maintain pre-GDUFA productivity		60% in 3 months*	75% in 3 months*	90% in 3 months*
Tier 1 minor amendments (4th – 5th)	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
Tier 2 amendment	Maintain pre-GDUFA productivity		60% in 12 months	75% in 12 months	90% in 12 months
Prior approval supplements	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
ANDA, amendment, and PAS in backlog on Oct 1st, 2012	Act on 90% by end of FY 2017				
Controlled correspondences	Maintain pre-GDUFA levels		70% in four months**	70% in two months**	90% in two months**

*10 months if inspection required

** One additional month added to goal if clinical division input required

GDUFA Hiring, procedural, & inspection performance goals

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Hire and train new staff	25% of total	50% of total	25% of total		
Type II DMF completeness assessment – conduct and publish list	★ →				
Enhanced refuse to receive standards for ANDAs and related submissions	→ ★				
Respond to appeals for ANDAs	Within 30 days of receipt				
ANDA teleconference requests	Maintain pre-GDUFA levels →		Close-out 200	Close-out 250	Close-out 300
Type II DMF teleconference requests	Maintain pre-GDUFA levels →		Limit one per DMF holder per month not to exceed ANDA teleconference levels		
Risk –adjusted biennial CGMP surveillance inspections of generic API and generic finished dosage form manufacturers	→				Parity of inspection frequency between foreign and domestic firms

GDUFA EFFICIENCY ENHANCEMENTS

ANDA and Type II DMF

- Issue complete response letters
- Use telephone information requests to address easily correctable deficiencies
- Issue DMF holder a letter once ANDA referencing DMF is approved or tentatively approved

Regulatory Science

- Develop an annual list of regulatory science initiatives
- Begin undertaking various regulatory science initiatives upon enactment of the program

Inspections

- Prioritize inspections of establishments associated with ANDAs that are otherwise approvable or eligible for tentative approval
- Make inspection classification results and date of the last facility inspection available to the public and industry on FDA's website
- Study foreign government regulator inspections, report findings publicly, and develop a program to utilize foreign inspections classifications when and where appropriate

Systems and Electronic Standards

- Develop API and FDF facility database for self-ID and that links facilities to DMFs and ANDAs
- Develop CMC records database to aid in the efficiency of review and inspection
- Develop and issue electronic data submission standards
- Enhance systems or build databases to implement program requirements

FY2014 USER FEES

Fee Type	GDUFA	PDUFA V
Application	$63,000	$2,169,000 (clinical) $1,084,000 (no clinical)
Supplement	$32,000	$1,084,000 (clinical)
FDF Facility/ Establishment	$220,000-$235,000	$555,000

GDUFA ALSO REQUIRES FACILITIES TO SELF-IDENTIFY

GDUFA Year 1
EXPECTED vs. RECEIVED

	EXPECTED	RECEIVED**
Original ANDAs	850* (750 from negotiations)	992
DMF CA	700* (Year 2 = 583)	1,580 (1_{st} QTR Year 2 = 241)
Controls	920 (5 year average)	953
PAS Supplements	576**	265

GDUFA Backlog (approx 3 yrs worth of receipts)
2,866 Original ANDAs; 1,868 PAS Supplements

* http://www.gpo.gov/fdsys/pkg/FR-2012-10-25/pdf/2012-26256.pdf (Fee Notice)

** http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384177.pdf (Report to Congress)

Highlights of GDUFA changes/challenges

Communications with Industry

- Complete Response (CR) Letters*
- Easily Correctable Deficiencies (ECDs)*
- Role of RPM
- Communication MaPP
- Status updates
- Pre-CR majors
- February Commissioned Corps Extra Duty
- Target Action Dates

*part of GDUFA commitments

Communications Practices

- **PAST:** Reactive, crisis management mode
  - Piece meal deficiencies – THIS IS ONE OF THE REASONS FOR GDUFA
  - Ad hoc, resource intensive, inadequately documented, differential treatment
  - Fishing expedition, shopping around
  - OGD "sold out" other Agency colleagues
- **NEED:** Fair, consistent, proactive, systematic **process** that meets goal dates
  - Ability to know where applications are in the review process and towards goal dates
  - Workload management

Complete Response Letters

- "Starting on October 1, 2012 … FDA will issue complete response letters, rather than discipline specific letters, for all ANDAs, including those pending…on October 1, 2012. Complete response letters will reflect division-level review of deficiencies from all relevant review disciplines, including inspections, and ….consults with other agency components..."

GDUFA Commitment letter, page 6.

Complete Response Letters

- Our goal is to issue CR that is as complete as possible
- Contains Major & Minor deficiencies
- No more piece meal deficiencies, i.e., no more discipline specific deficiencies
- Required internal processes & policy & training

- Major paradigm shift
  - FDA
  - OGD
  - Industry

Easily Correctable Deficiencies (ECD)

- "FDA reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in the ANDA..."

GDUFA Commitment letter, page 6.

Easily Correctable Deficiencies (ECD)

- Goal is to allow reviewer to complete review
- No definition in Commitment Letter
- If minor/major deficiency, it is **NOT** an ECD
- Needed to revise internal processes
  - Guidance Major/Minor/Telephone Amendments, 2001
  - MaPP 5240.7, 2003
  - Internal CR IQP/SOP, 2010(?)
- Need to define, create policy, train and implement

Regulatory Project Manager (RPM)

- Previous OGD Project Mgmt siloed with minimal staffing compared to need
- No one responsible for application from door to door
- No central point of contact
- Imperative need to meet GDUFA goals
- **#1 "Lessons Learned" from PDUFA implementation**

Regulatory Project Manager (RPM)

- **"THE"** Point of Contact is the Regulatory Project Manager
  - Centralize Communication Flow vs. past Siloed practices
  - Good communication practices
  - Consistency
  - Streamlines
  - Documentation of communication
- Allows reviewers to **REVIEW**
- Consistent with FDA practices with other product Centers and other User Fee Programs

Status Updates

- FDA recognizes the importance of these and industry desire to launch on Day 1
- We value constructive input and collaboration
- We are working with GPhA
- We have been responsive
- Moving toward predictability

FEBRUARY:

Extra Duty with OGD Commissioned Corps Officers

- Sending status updates for all ANDAs received to date
- Update on where each discipline is
- Substantial effort
- Over 3,500 application updates
- One time
- Above and beyond GDUFA

IMPLEMENTING INTERNAL GOAL DATES "Target Action Dates"

- Assign "Target Action Dates" first (high priority ANDAs)
- Acclimate staff to work with GOAL dates
- Monitor success in achieving dates
- Once predictable, apply to ALL applications
  - Backlog + Years 1 & 2
- Transition to communicating "Target Action Dates" (+/- processing times) to ANDA holders
- Goal dates = HUGE paradigm shift for OGD

CHAOS

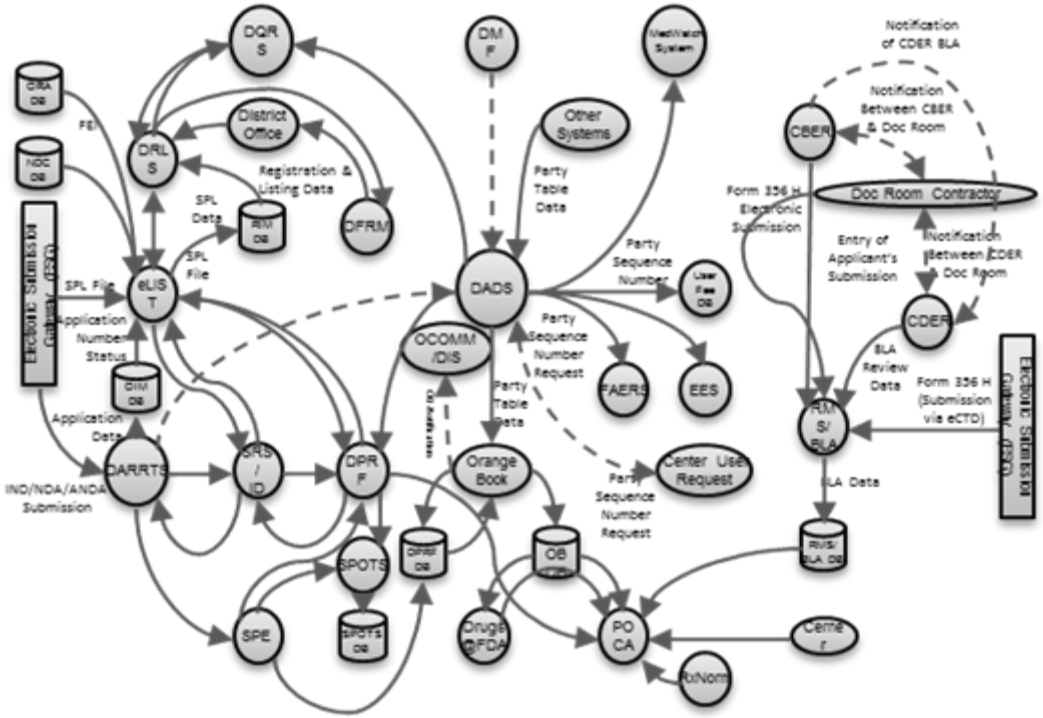
REACTIVE

PROACTIVE

TARGET ACTION DATES & GOAL DATES (PREDICTABLE)

IT Current State: PROBLEMS

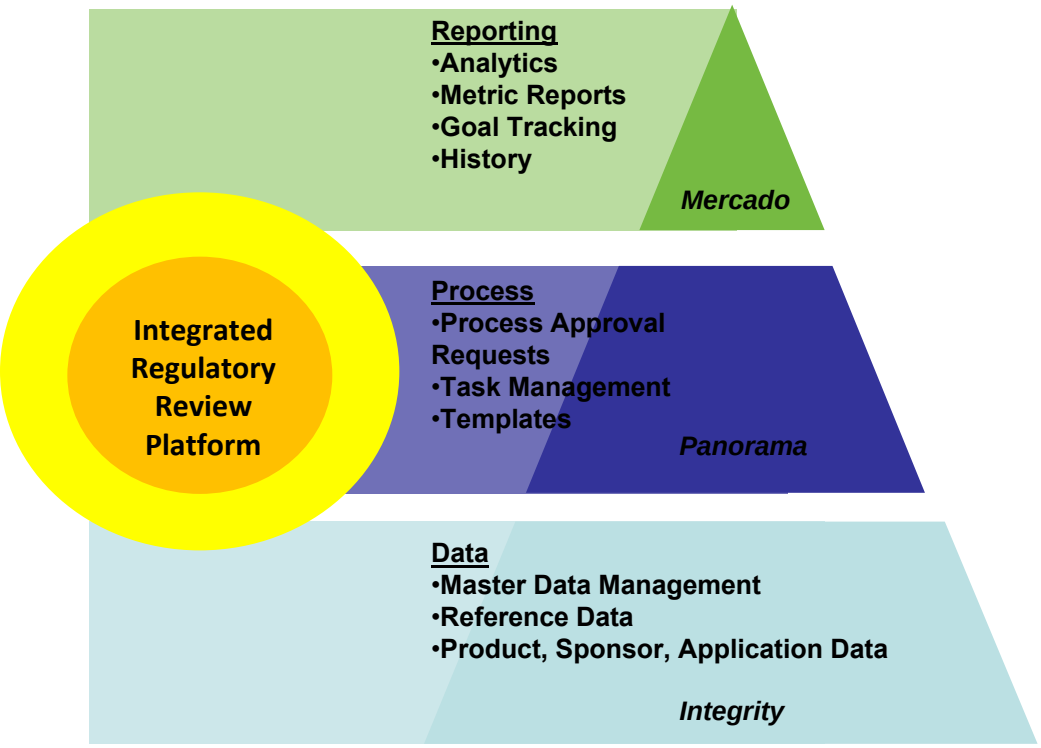
Individual Data Repository → Individual System Analytics → Multiple Reporting Methods → Major Challenges



- Inconsistent Terminologies
- Not User Friendly
- Not Flexible
- Fragmented Data Sources

IT Future State: Enhanced IT Systems & Technology

"Getting to 2017"



Value to OGD:

- The ability to measure progress against goal dates
- Real-time visibility into queue and status of applications and reviews
- End-to-end support of the generic drug application review process
- Reduction of manual and/or duplicate entry
- Integrated searchable data, dynamic integrated reporting
- Visibility patent and exclusivity status, site inspection history, and standardized communications documents

Value to the Organization:

- Improved planning and forecasting
- Consistent data and consistent communication
- Structured reporting tools
- Greater predictability and transparency of the generic drug review process
- More efficient service to the public
- Integration of process and technology

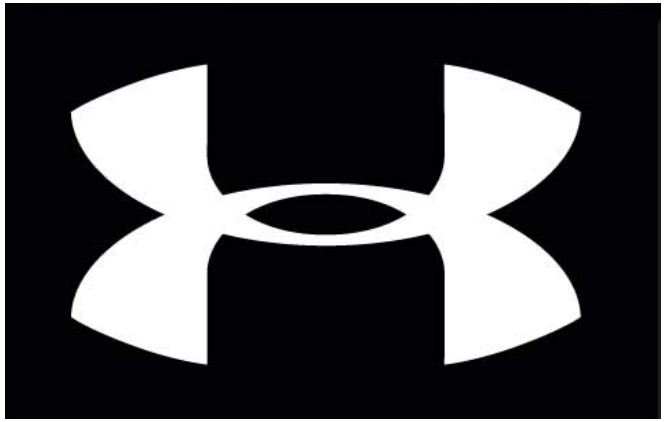
INDUSTRY CHANGES

INDUSTRY CHANGES

- GDUFA is a commitment between FDA and Industry
- Requires changes to both parties

- What is industry doing because of GDUFA?
- Learning, training, policies, practices?
- How will that get us to meeting our goals?

Business Practices



- **Supply Chain Integrity**
- **Application Chain Integrity**

1. **Demand accountability from your contractors** (API manufacturers, suppliers, sites)
   - Knowledge about inspections
   - Knowledge about any changes, e.g., DMF supplements
   - Knowledge about correspondence from FDA, e.g., deficiencies
   - Confidentiality agreements, LOA, +++
   - Who is on the arrears list

2. Expect that your regulatory experts understand GDUFA

- Have they read the GDUFA goals/commitment letter?
- Electronic submissions only for GDUFA goals
- Ensure that 356h submission is accurate, complete, and identifies all sites

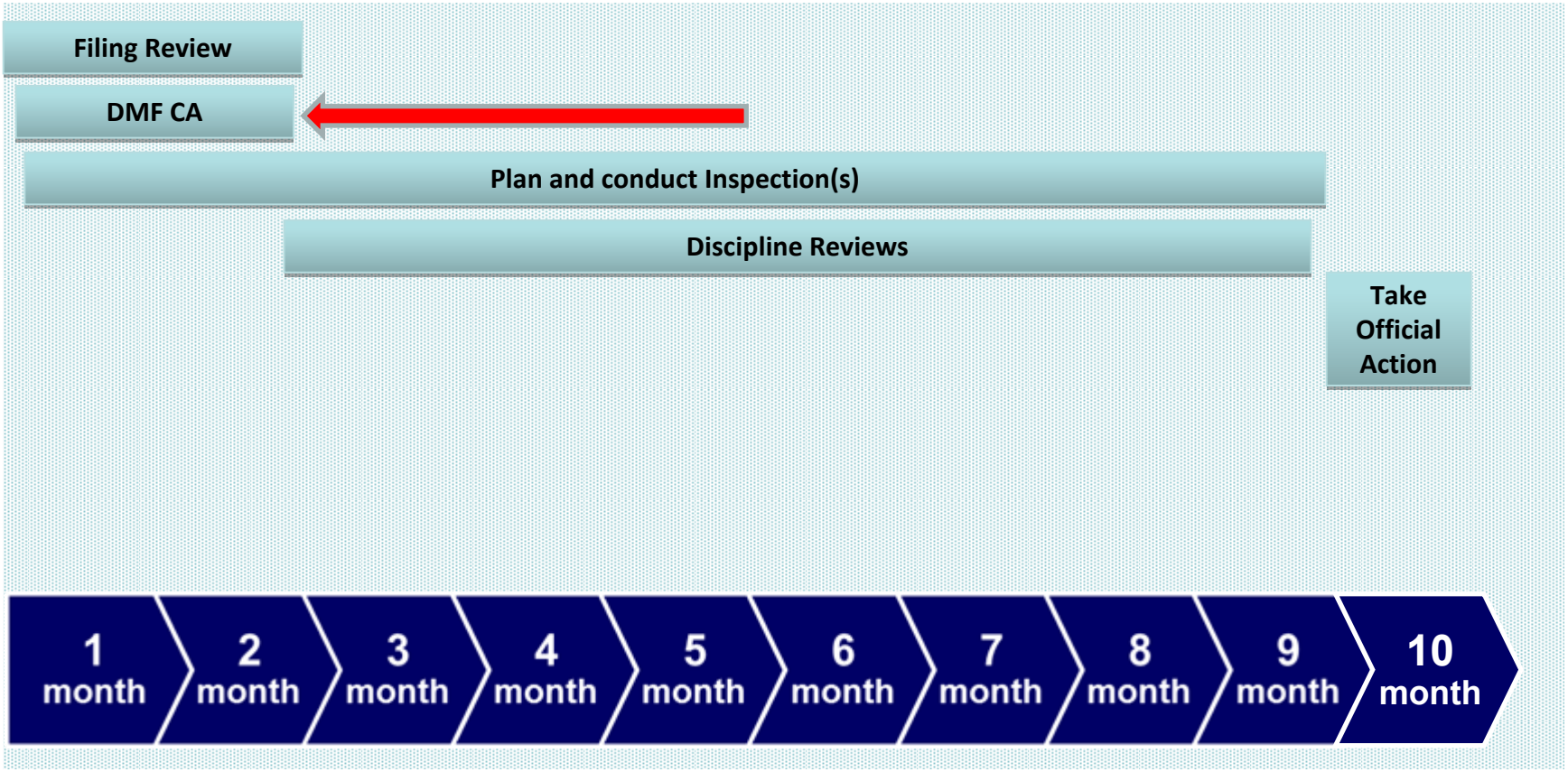
  (this is critical for inspection parity)
- ALL submissions appropriately labeled as to what type they are

3. Get DMF Completeness Assessment <u>before</u> ANDA submission

- DMFs should be submitted well in advance of ANDA in order for CA to be conducted
- Submit ~6 months in advance
- Allows time for industry to respond to DMF incomplete letter

- GDUFA Years 1 & 2 – industry has gotten a free pass being able to submit DMF with ANDA.
- GDUFA Year 3 and beyond – **<u>probably get RTR</u>**

Simplified ANDA review process



4. Complete Response (CR) letters

- Adequate response addresses ALL deficiencies received in the CR
- Partial response will not be accepted
- Appropriately labeled submission (CR)
- Timely response
  - Within 1 year
  - Per 21 CFR 314.65 FDA will start process to administratively withdraw applications
  - O/w abusing the system, distorting time to approval metrics, and wasting GDUFA resources

Complete Response (CR) letters

- "Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65..."

- FDASIA requirement to report number of days applications are **pending** with industry & with FDA

5. Easily correctable deficiency (ECDs)

- Timely response
- Appropriately labeled submission (ECD)
- Allows OGD reviewers to finish their reviews
- Moves us toward being able to issue action
  - CR, TA or approval
- Still may get major/minor deficiencies in CR

6. Getting approved when you expect/want it

- When did you last communicate with FDA?
- Does the Agency has all legal documents, court findings, agreements, etc.?
  - Should update these every 6 months
- Did you previously get TA? Since then, what changes have been made?
  - API supplier, process (API or FDF) changes?
  - All changes need to be submitted, and are likely to trigger new reviews. FDA needs lead time to review all changes

7. Improve submission quality

- Industry Motto: File First, Develop Later
  - Poorly assembled applications
  - Poor quality applications
  - Leading to multiple-cycle reviews
  - FDA reviewers serve as “consultants” to industry and product development
- Inefficient use of GDUFA resources

ANDA AMENDMENTS

	Solicited Amendments Goals	Unsolicited Amendments Goals
TIER 1	1st Major: 10 months 1st – 3rd Minor: 3 months 4th & 5th Minor: 6 months	Delaying action*or otherwise would eventually be solicited: 3 months
TIER 1	Any TIER 1 amendment requiring an inspection: 10 months	
TIER 2	N/A	Amendment not arising from "delaying action": 12 months
TIER 3	≥ 2nd Major: No goal ≥ 6th Minor: No goal	N/A

*Indicated by sponsor and agreed by FDA

GDUFA Accomplishments

Industry Accomplishments

- Fees paid
- Self identification
  - ~2,200 sites
  - Foreign > domestics sites
  - API > FDF
- **THANK YOU!**

FDA Accomplishments

- **FDA HIT ALL YEAR 1 DELIVERABLES**

GDUFA Hiring & Training

- Year 1 Goal: hire 25%
- FDA met and exceeded hiring goals

- Year 2 Goal: hire 50%

- OGD alone:
  - Year 1 ~140 FTEs (65 were CMC)
  - Year 2 >200 FTEs (+~140 CMC to OPS/OPQ)

Approvals & Actions

	FY2012	FY2013*	FY2014 (1st QTR)**
Original ANDAs	500	440	90
PASs	260	540	120
TAs	100	95	30
CRs	<50	>1,200	350
	~900	**~2,300**	

*http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384177.pdf (Report to Congress
**OGD Receipts & Actions:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm375079.htm Numbers are rounded and do not reflect actual numbers for Congressional reporting purposes

GDUFA BACKLOG

- 2866 original ANDAs
- 1882 PAS supplements

First Actions in FY2013

(reportable metric)

>1,600 actions issued (~35%)

- CR with inspection (#1)
- Approval or TA (#2)
- RTR
- Withdrawal

NOW: ~45% of backlog has a first action

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384177.pdf (Report to Congress

GDUFA COMMUNICATIONS

- Complete Response Letters for ANDAs
- Total CRs Issued ~1,250
  - Majority were for GDUFA backlog 1st action
  - ~560 with inspections
  - ~690 **WITHOUT inspections**
    - Are not part of GDUFA metrics/commitments
    - Communication & Transparency with industry

OGD Receipts & Actions:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm375079.htm

GDUFA COMMUNICATIONS

- FDA - GPhA Board of Directors Quarterly meetings

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandageneric s/ucm370616.htm

ACCOMPLISHMENTS:

GDUFA FY2013 Regulatory Science

- Only user fee program with Regulatory Science
- New External & Internal Collaborations
  - 20 Grants, 8 Contracts
  - Rapid Response Capabilities (equipment + fellows)
- ~ $20 million
- May 2013, Part 15 for public input on FY2014 GDUFA regulatory science priorities
- FY2014 – Part 15 – stay tuned

http://www.fda.gov/Drugs/NewsEvents/ucm367997.htm
http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm

POLICY ACTIVITIES

- GDUFA Requirements
- GDUFA related
- Non-GDUFA
  - BE
  - CMC

GDUFA GUIDANCES

- GDUFA Questions & Answers x 2
- DMF Completeness Assessment
- Refuse to Receive
- Fee Types

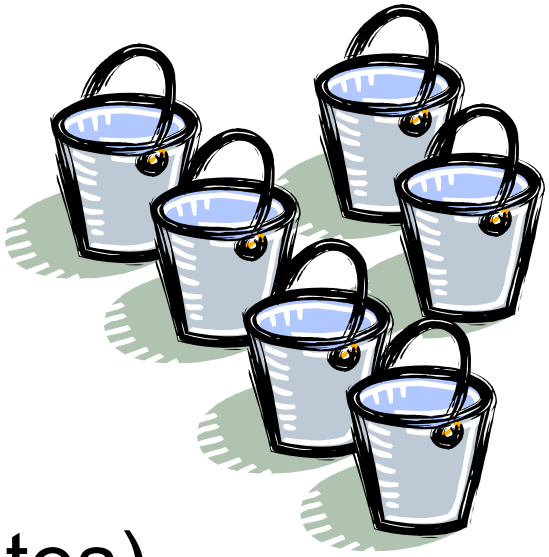
- FDA issued ALL guidances required under GDUFA

GDUFA-Related Policy Activities

- MaPP on Prioritization Policy
- How to improve quality of applications
  - FR notice January – need industry input
- https://www.federalregister.gov/articles/2014/01/23/2014-01309/improving-the-quality-of-abbreviated-new-drug-application-submissions-to-the-food-and-drug
- Moving from TA to Approval
- Supplements & Tiered Amendments
- Controlled Correspondence

Prioritization Policy

- PIV
- PEPFAR
- Drug Shortage
- GDUFA backlog
- Year 1 & 2 cohorts (no goal dates)
- Years 3, 4, & 5 cohorts (goal dates)
- Public health need
- Congressional interest



Non-GDUFA GUIDANCES: BE

- NEW BE guidances ~60
  - Key Products:
    - Albuterol sulfate
    - Buproprion Hydrochloride
    - Ferumoxytol
    - Fluticasone propionate/salmeterol xinafoate
    - Sodium ferric gluconate
- Revised BE guidances - ~40
- General BE guidance (published December 2013)
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf

Non-GDUFA Policy Activity: CMC

- Guidances:
  - Stability Guidance & accompanying Q&A
  - Tablet Size & Shape
  - Tablet Scoring
- Other Policy Activities:
  - Inactive Ingredients Database (IID)
  - CMC Changes in Annual Report (AR)
  - PAS
- CMC Guidances will be OPS-OPQ's responsibility, not OGD

OGD UPDATES

OGD Priorities

1. GDUFA

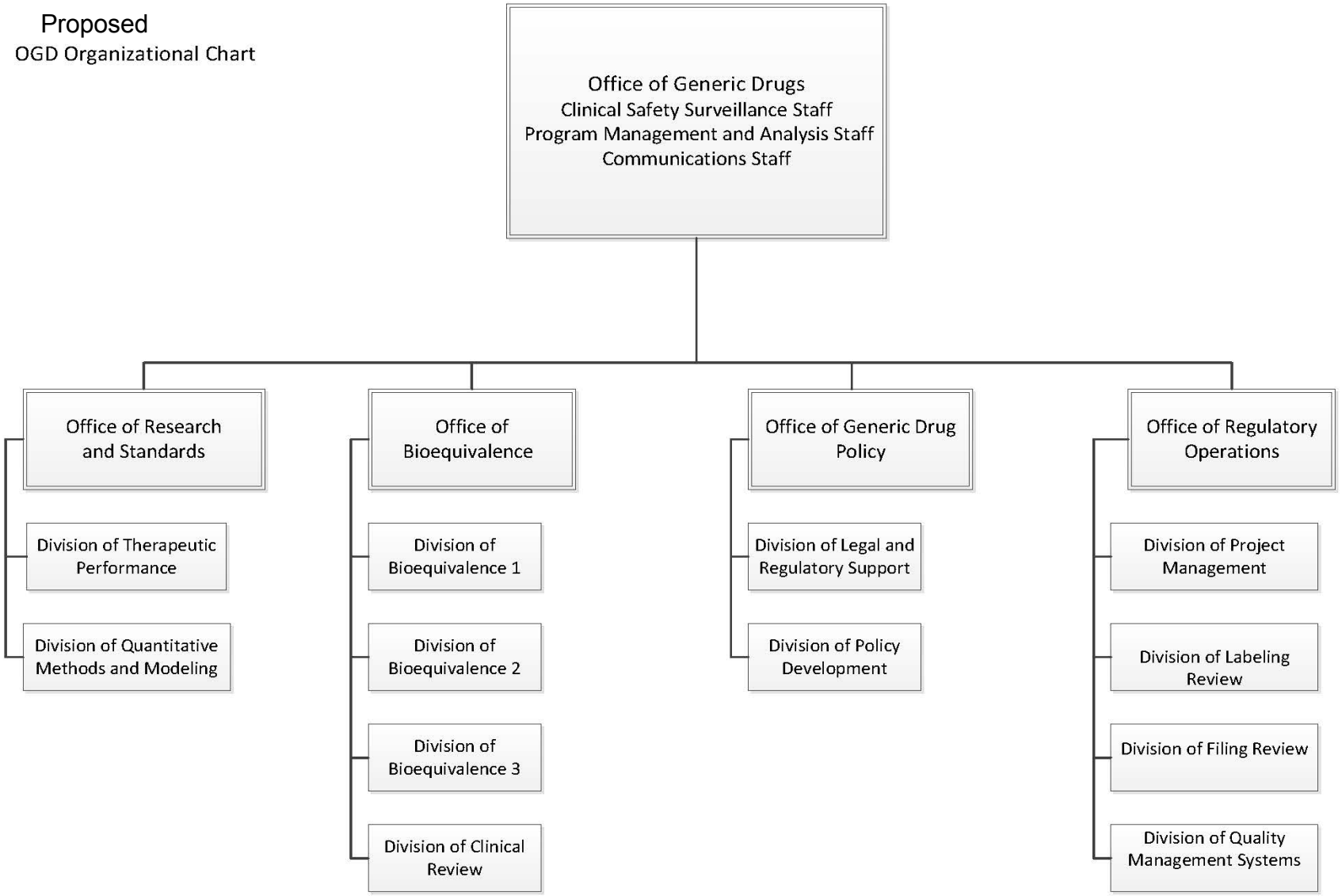
2.GDUFA

3.GDUFA

Major Reorganizations

- OGD reorg to a Super Office
- OPQ reorg
  - All CDER product quality reviews
  - OGD chemistry and microbiology review functions

Proposed
OGD Organizational Chart



OGD CHALLENGES

1. GDUFA implementation
2. OGD Reorg
3. Move to White Oak (Spring 2014)

Hiring under GDUFA
Training new hires
Identifying key leadership
Budget changes
Office space

Workforce Development
Cultural Change Mgmt

Why do we have to get it right with GDUFA?











IMPLEMENTING GDUFA is a shared responsibility

Urgency
Ownership
Accountability
Commitment

THANK YOU!